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Adult neuroplasticity: A new “cure” for major depression?

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Neuroplasticity involves synaptic reorganization (Box 1) in response to environmental stressors or rewards and is thought to underlie our ability to adjust, learn and remember.⁷ However, in mental illness, it is thought that maladaptive plasticity occurs, resulting in persistence of the depressive symptoms, such as rumination, anhedonia and others.⁸ By harnessing corrective neuroplasticity (Box 2), it may be possible to reprogram the maladaptive behaviour and produce long-lasting remission. This editorial presents evidence that both pharmacological and brain stimulation antidepressant approaches may act by inducing corrective neuroplasticity to mediate remission. Increasingly, antidepressant effects on neuroplasticity are shown to correlate with behavioural improvement, both in humans¹⁸ and in animal models,¹⁹ raising the possibility that neuroplasticity could provide a new avenue for depression research. However, learning how to harness this capacity to enhance recovery remains a challenge.

Measures of neuroplasticity in human depression

In clinical studies, grey matter volume obtained from MRI provides an indirect indicator of neuronal density. Changes in grey matter volume are thought to reflect neuroplasticity (Box 1). But what is grey matter volume measuring? In major depressive disorder (MDD), it is clear that there is both a reduction in grey matter volume (especially in the subgenual anterior cingulate cortex²⁰ and hippocampus²¹) and, from postmortem studies, a loss of both neurons and glia, particularly in those with chronic illness.^{22,23} Reduction in hippocampal volume in depression has been correlated with severity of memory impairments.²⁴ In chronic social defeat mice, volume changes were region-specific and correlated inversely with social interactions.²⁵ Reductions in hippocampal volume were also seen in a social depression model in female cynomolgus monkeys,^{26,27} which also showed reductions in serotonin 1A (5-HT_{1A}) receptor levels.²⁸ These grey matter volume reductions correlated with reduced cell numbers, predominantly of astroglial and granule cells, and with reduced cell

Box 1: Defining neuroplasticity

Neuroplasticity is a broad term, so how do we define it? At a systems level, it can encompass several discrete structural modifications that rewire the brain, ranging from early synaptic plasticity, either strengthening (long-term potentiation) or weakening (long-term depression) synaptic transmission; synapse formation or retraction; spinogenesis; synaptogenesis (also termed late synaptic plasticity); axonal sprouting; axon regeneration; dendrite growth and formation;¹ and even neurogenesis.^{2,3} Synaptic plasticity is defined as a change in synaptic efficiency, but this sometimes includes formation of new synapses underlying late forms of synaptic plasticity.⁴ For the present discussion, neuroplasticity is as classically defined at a cellular level to denote structural change in neurons,⁵ thus excluding early synaptic plasticity and neurogenesis. In the context of brain imaging, the term neuroplasticity is applied to persistent or stable changes in brain functional activity (functional connectivity) or structure (grey matter volume) that are thought to be the result of cellular neuroplasticity.⁶

Box 2: Triggers for adult neuroplasticity

Initiation of neuroplasticity involves changes in neuronal activity. Neuronal activity triggers signalling pathways, including ERK1/2⁹ and CREB signalling,¹⁰ leading to increased release of trophic factors, such as brain-derived neurotrophic factor⁴ or vascular endothelial growth factor,¹¹ which in turn trigger transcriptional changes¹² that, if stimulation is persistent, result in structural changes, including formation of dendritic spines and recruitment of nerve terminals, resulting in new synaptic contacts.¹³ For example, exercise-induced behavioural improvement and neurogenesis are reduced in brain-derived neurotrophic factor (Met/Met) mutant mice.¹⁴ Some forms of plasticity (synapse reorganization) can occur in response to various stimuli, including drugs, exercise and enriched environment.¹⁵ However, different signalling pathways may trigger axonal sprouting or regeneration. Axonal regeneration in the adult central nervous system is fairly uncommon, but does occur in a subset of nonmyelinated axons, such as those of the serotonin system.¹⁶ Axonal sprouting is often triggered by neuronal activation following a brain injury, such as stroke, due to a loss of contralateral inhibition.¹⁷ It remains unclear whether axonal regeneration or sprouting play a role in the treatment of major depression, but these processes may occur in poststroke depression, where axonal projections are damaged.

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and neuropil volumes mainly in the anterior hippocampus.²⁹ In humans, the postmortem hippocampus of individuals with major depression showed similar reductions in both granule cell and astroglial cell numbers and reductions in cell and neuropil volumes.³⁰ Reductions in hippocampal volume have also been associated with childhood maltreatment,³¹ a major risk factor for psychiatric disease and suicide. These studies showing reduced cell numbers and neuropil and grey matter volumes indicate an impairment of developmental or adult neuroplasticity in MDD. The causes of impaired neuroplasticity in MDD are unclear, but chronic increase in stress hormones replicates the reduction in hippocampal neuropil and is a likely culprit.³² Animal studies suggest that these stress-associated neuroplasticity processes may be prevented or reversed by antidepressant induction of neuroplasticity mediators such as neuritin;³³ however, the mechanisms involved remain unclear (Box 2). Increasing evidence points to stress-induced microglial activation as a key contributor to synaptic remodelling,^{34–37} but how antidepressants or brain stimulation affect microglial responses in humans is unclear.

In order to assess functional neuroplasticity in humans, various brain stimulation approaches have been used, including paired associative stimulation (PAS) or transcranial magnetic stimulation (TMS). Depressed individuals show reduced PAS in the dorsolateral prefrontal cortex (DLPFC) compared with healthy individuals, suggesting reduced neuroplasticity.³⁸ Selective serotonin reuptake inhibitors (SSRIs) affect neuroplasticity induced by transcranial direct current stimulation (tDCS), as detected by repetitive TMS (rTMS)-evoked motor cortex responses or PAS responses.^{39–41} Recently, magnetic seizure therapy has been shown to provoke changes in the excitability of the frontal cortex that correlate with a reduction in suicidal ideation.⁴² It is hypothesized that by targeting areas that are most inactivated in MDD with chronic brain stimulation (e.g., rTMS), a more effective and sustained antidepressant response may be attained.⁴³ Thus, sustained antidepressant responses may be driven by stimulation-induced synaptic reorganization.

Serotonin and adult neuroplasticity

Most antidepressants target monoamine reuptake, and SSRIs block the 5-HT transporter specifically.⁴⁴ Recent postmortem studies show that in addition to reductions in grey matter volume, MDD is associated with reduced 5-HT innervation of the orbitofrontal cortex.⁴⁵ The mechanisms underlying this deficiency are unclear. In this regard, impaired protein translation triggered by the cytokine tumour necrosis factor- α has been implicated in a reduction in 5-HT neurons and 5-HT-induced excitatory PFC responses associated with SSRI-resistant depression-like behaviour in mice.^{46,47} Given the role of 5-HT in SSRI action and the capacity of SSRIs to alter adult neuroplasticity in animal models via 5-HT_{1A} receptors,^{48,49} recent studies in humans have correlated grey matter volume with levels of 5-HT receptor binding detected using positron emission tomography or by measuring white matter density using diffusion tensor imaging (DTI). In healthy individuals, 5-HT_{1A} receptor binding was

correlated with grey matter volume in several regions, including the hippocampus and PFC,⁵⁰ while this correlation was lost in those with MDD, in whom a correlation with raphe (presynaptic) 5-HT_{1A} receptors emerged in restricted cortical areas.⁵¹ These correlations suggest an uncoupling of postsynaptic 5-HT_{1A} receptors and a predominant role of presynaptic 5-HT_{1A} autoreceptor-mediated inhibition of neuroplasticity in MDD. Interestingly, in MDD, the regional 5-HT_{1A}-cortical thickness association correlated with the number of tracts from midbrain to specific cortical regions seen using DTI.⁵² This suggests that a strong interaction of 5-HT projections with the default mode network may drive increased rumination associated with MDD.⁵³ Taken together, these and other studies implicate the 5-HT system in changes in neuroplasticity occurring in major depression.

Recently, a receptor-mediated mechanism has been identified that could underlie SSRI-associated cortical neuroplasticity, which involves 5-HT₇ receptor signalling to activate metalloproteinases to mediate synapse formation.⁵⁴ In the mouse chronic social defeat model, alterations in excitatory/inhibitory input to 5-HT neurons and of synapse size and number in the hippocampus were reversed by chronic deep brain stimulation in parallel with its antidepressant actions.⁵⁵ These results in mice suggest that activation of 5-HT neurons can trigger neuroplasticity of the 5-HT system. In this regard, an increase in cortical thickness seen upon acute (1 wk) SSRI treatment was associated with increased response (at 8 wk) in MDD.⁵⁶ In humans, successful treatment with rTMS has been shown to increase hippocampal volume and is associated with cognitive improvement in depressed patients.⁵⁷ Interestingly, the combination of SSRI and anodal tDCS stimulation enhanced memory function, while either treatment alone was ineffective.⁵⁸ Thus, combining brain stimulation with SSRI treatment to increase 5-HT neurotransmission could be a promising approach for treatment-resistant depression.

Ketamine and adult neuroplasticity

Acute treatment with low-dose ketamine has been shown to produce rapid (within 1 h) improvements in treatment-resistant MDD,^{59,60} particularly in reducing suicidality.⁶¹ Ketamine acts like brain stimulation to increase glutamatergic activity (glutamate surge) inducing brain-derived neurotrophic factor release to trigger the formation of new dendritic spines.⁶² However, owing to risk of psychosis, it is used only acutely, but recent trials suggest that repeated ketamine administration may be effective and safe for treatment-resistant depression.^{63–65} It also remains unclear to what extent ketamine's antidepressant actions in humans depend on neuroplasticity. In rodents, inhibitors of the mammalian target of rapamycin that reduce dendritic protein synthesis prevent ketamine-induced neuroplasticity and behavioural improvement,⁶⁶ suggesting a role for neuroplasticity, although additional mechanisms are implicated in ketamine action.⁶⁷ Whether ketamine could "kick-start" the response to SSRI treatment has not been studied extensively, although initial results suggest improved response and remission rates compared with placebo.⁶⁸

Conclusion

Evidence from animal models of depression and increasing, but indirect evidence from human studies suggest that neuroplasticity is impaired in MDD. Both in humans and in animal models, treatment with brain stimulation (ketamine, DBS, or other methods) induces regional increases in grey matter volume that are associated with antidepressant response. These brain volume changes involve structural neuroplasticity mechanisms, such as dendritic spinogenesis, synaptic reorganization, or axonal sprouting or regrowth. In humans, SSRIs, brain stimulation or their combination may enhance adult neuroplasticity to mediate recovery in MDD. However, it remains to be elucidated what is the exact role of impaired neuroplasticity in human depression and whether triggering neuroplasticity could accelerate or potentiate antidepressant responses.

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